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13. ABSTRACT (Maximum 200 Words) High circulating levels of insulin-like growth factor 1 (IGF-1) or low levels of 1,25(OH) ₂ vitamin D (1,25(OH) ₂ D) are associated with an increased risk of prostate cancer. This project examines whether specific dietary patterns are related to prostate cancer by influencing levels of IGF-1 and 1,25(OH) ₂ D; specifically whether high energy and protein intakes increase IGF-1 and high intakes of calcium, phosphorus, and animal protein decrease 1,25(OH) ₂ D levels. The relationships between dietary factors and circulating IGF-1 and 1,25(OH) ₂ D are being examined using the Massachusetts Male Aging Study, for which dietary data and blood samples have already been collected. Laboratory analyses for serum 1,25(OH) ₂ D and IGF-1 levels are nearly completed. After examining the relation between the dietary factors and serum level, we will use these data to formulate a predicted 1,25(OH) ₂ D or IGF-1 score for men in the Health Professional Follow-Up Study based on their responses to a dietary questionnaire. We will thus be able to examine the predicted impact of the combined effect of pertinent dietary factors in relation to prostate cancer risk for the 1,600 cases of prostate cancer that have occurred in this cohort. Ultimately, our aim is to understand how specific dietary factors influence development of prostate cancer.				
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FOREWORD

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N/A In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

X For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

N/A In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

N/A In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

N/A In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Edward Giovanni 10/29/89
PI - Signature Date

TABLE OF CONTENTS

Front Cover	page 1
SF 298	page 2
Foreword	page 3
Table of Contents	page 4
Introduction & Body	page 5

The scientific rationale for this Idea Grant to clarify determinants of levels of IGF-1, IGFBP-3, 1,25(OH)₂ vitamin D (1,25(OH)₂D) and 25(OH)vitamin D has increased since the initial proposal. Additional studies supporting an association between calcium intake and prostate cancer risk (1), and between IGF-1 and prostate cancer risk (2) have recently been published. In particular, interest in the area of IGF and cancer has blossomed quite recently, as evidenced by the convening of the First International Workshop on "Growth Hormone, Insulin-like Growth Factors and Neoplasia" held recently in Boston (October 24-25, 1999). There is clearly a need to determine factors, particularly modifiable ones, that impact on levels of these hormones that influence prostate carcinogenesis.

For year 1, our primary goals were the preparation and shipment to laboratories (months 1-3) of serum samples collected from men in the Massachusetts Male Aging Study (MMAS), laboratory analyses (months 4-10), data receipt and cleaning (month 11), and beginning data analyses (month 12-). The first task has been completed. Specifically, 630 specimens were retrieved, thawed, and aliquotted from MMAS serum samples that have been stored in freezers in the laboratory of Dr. C. Longcope at the University of Massachusetts, Worcester. The samples were then shipped by overnight courier to Dr. Michael Pollak at McGill University in Canada, and Dr. Bruce Hollis at the Medical University of South Carolina. Because a higher than expected number of samples with insufficient volume were found, 630 rather than the projected 900 samples were sent to the laboratories. This number was lower than the 900 samples that had been anticipated. However, this is not expected to adversely effect the conduct of the study appreciably, particularly because of the high quality control of the laboratories (see below).

For months 4-10, the main goals were the determination of concentrations of IGF-1, and IGFBP-3 by radioimmunoassay in the laboratory of Dr. Pollak, and the determination of concentrations of 25(OH)D and 1,25(OH)₂D by radioimmunoassay in the laboratory of Dr. Hollis. These analyses are ongoing in both laboratories and are nearly completed. Although we had planned on these assays being completed by the end of month 10, we are several months behind the initial schedule. However, we do not anticipate that this would delay the ultimate completion of the study, as year 2 is composed primarily of data analysis and manuscript preparation, and efforts can be intensified in these areas.

Thus far, in the ongoing laboratory analyses in the two laboratories, no unanticipated problems have been encountered. In fact, the quality control in both laboratories appears to be outstanding. For the most recent samples we have sent to these laboratories (from separate projects), the coefficients-of-variation (CV%) were 5.4% for 25(OH)D, 5.3% for 1,25(OH)₂D, 2.6% for IGF-1, and 3.5% for IGFBP-3. These are considerably better than had been reported in the initial proposal (8% for IGF-1 and 6% for IGFBP-3, unavailable at the time for 25(OH)D and 1,25(OH)₂D). The excellent CV% is especially noteworthy for 1,25(OH)₂D because it is at low concentrations in the plasma (1000-fold lower than 25(OH)D). The better than anticipated CV% in both laboratories

helps offset the reduced number of analyzable specimens because the power to detect correlations is determined both by the sample size and by the accuracy of the laboratory assay.

For year 2, we expect to meet our goals of (1) the assessment of dietary (total energy, fat, protein, alcohol) and other modifiable (e.g., physical activity) and nonmodifiable (e.g., body habitus at various ages, height) risk factors for prostate cancer as predictors of IGF-1 and BP-3, and the evaluation of the rate of decline of IGF-1 (two measures 10-years apart) by age and predictors of rate of decline; (2) statistical analysis of dietary (e.g., calcium, phosphorus, fructose, animal protein) and other modifiable risk factors for prostate cancer predicting concentrations of 1,25(OH)₂D and 25(OH)D; (3) statistical analysis of correlation between prostate-specific antigen (PSA) at time 1 (T1) and time 2 (T2) and IGF-1 and 1,25(OH)₂D; and (4) the examination of risk of total and metastatic prostate cancer in a second cohort, the Health Professionals Follow-up Study, using levels of IGF-1 and 1,25(OH)₂D predicted from the empirical model of dietary predictors of these circulating factors derived in this study.

In keeping with the original timeline put forth in the Statement of Work, we have yet to begin the analyses. Therefore, there are no Key Research Accomplishments or Reportable Outcomes at this time.

REFERENCES:

1. Chan JM, Giovannucci E, Andersson S-O, Yuen J, Adami H-O, Wolk A. Dairy products, calcium, phosphorous, vitamin D, and risk of prostate cancer. *Cancer Causes Control* 1998;9:559-566.
2. Wolk A, Mantzoros CS, Andersson S-O, Bergström R, Signorello LB, Lagiou P, Adami H-O, Trichopoulos D. Insulin-like growth factor 1 and prostate cancer risk: a population-based, case-control study. *J Natl Cancer Inst* 1998;90:911-915.